REMARKS/ARGUMENTS

Claims 1-13 and 21 were pending. Claims 1, 3-7 and 13 have been amended. Claims 22-26 are added. Claims 2, 8-12, and 14-21 are canceled. No new matter is added.

Claims 1-12 have been rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Office Action states that the application lacks description for synthesis of all biological macromolecules.

Claims 1, and 6-12 are stated to be genus claims in terms of a method of synthesizing any biological macromolecules *in vitro*. Claims 1-7 are genus claims in terms of a method of synthesizing a biological macromolecule where oxidative phosphorylation is activated by any means.

Without conceding to the correctness of the rejection, and retaining the right to refile claims of original scope, Claim 1 has been amended to recite the synthesis of polypeptides or polynucleotides, both of which are supported by experimental data provided in the application. Withdrawal of the rejection as it is applied to a method of synthesizing any biological macromolecule is requested.

The Office Action further states that the application lacks description for any method of activating oxidative phosphorylation in an *in vitro* synthesis method. Applicants respectfully submit that the present invention is a pioneering step in the development of cell-free synthesis reactions. By careful development of techniques, Applicants have provided for a result that significantly enhances the ability of the art to commercially produce proteins in a cell-free system.

Prior to the present invention, one of skill in the art did not conceive of oxidative phosphorylation as possible in a cell-free system. However, in view of Applicants remarkable discovery, one of skill in the art is now informed that such is possible, and can freely make minor changes in the reaction conditions so as to mimic the results of the present invention. Such minor modifications require no undue experimentation, in view of the data provided herein.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

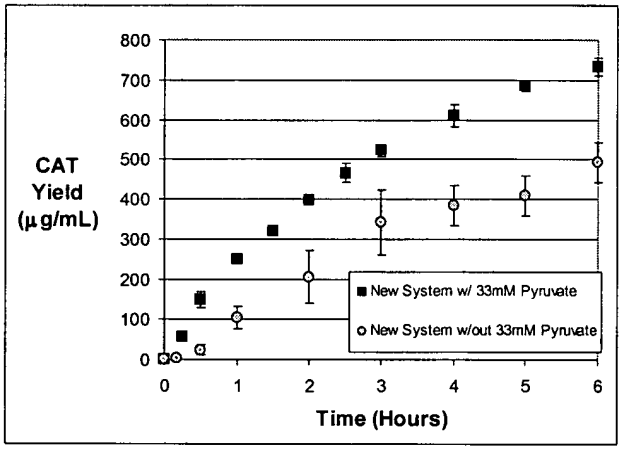
Claims 1-12 and 21 have been rejected under 35 U.S.C. 112, second paragraph as indefinite in the recitation of the term "enhanced". The rejected claim language has been deleted from the claims. Withdrawal of the rejection is requested.

Claims 1-6 and 8-10 have been rejected as anticipated by Kim et al. (200). The Office

Action states that Kim *et al.* teach a method of synthesizing biological macromolecules in a reaction mix comprising an extract from *E. coli* grown in glucose and phosphate containing medium and comprising magnesium at a concentration of 16 mM.

Applicants respectfully submit that the presently claimed invention is not anticipated by the cited art. Claim 1 has been amended to recite that polypeptides are synthesized in the reaction mixture in the absence of an exogenous energy source.

The Examiner's attention is drawn to the data presented in Figure 1 of the present application, which is reproduced below.



These data clearly demonstrate that protein synthesis readily occurs in the absence of an exogenous source of energy, although the addition of pyruvate provides for an improvement in yield. These data may be viewed in the context of Applicants' Figure 2:

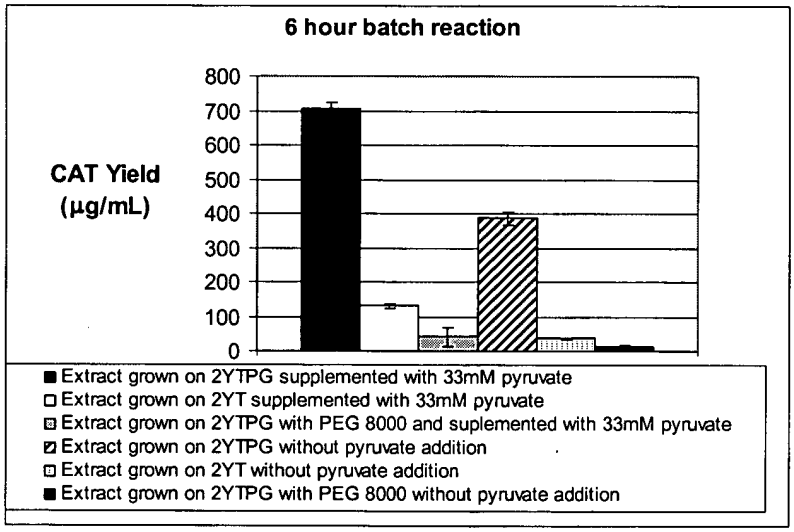


Figure 2 demonstrates a dramatic difference in protein synthesis in the absence and presence of polyethylene glycol (PEG). It can be seen that in the presence of PEG, there is virtually no

synthesis in the absence of pyruvate.

In the prior art, as stated in paragraph 2.1 (page 28), the reactions were performed in the presence of 2% polyethylene glycol. As shown by Applicants, under these conditions there is no protein synthesis in the absence of exogenous energy sources, and thus oxidative phosphorylation is not activated.

The data provided by Applicants is further supported by the findings of Kim *et al.*, as shown in Table 1 of the reference. Table 1 shows the effects of adding various supplements to the reaction mix, where the only significant increase in expression was found where phosphoenol pyruvate (a commonly used exogenous energy source), thereby further supporting Applicants' position that the prior art does not teach a method of polypeptide synthesis here oxidative phosphorylation is activated.

The rejection of Claims 21 is made moot by the cancellation of the claim.

Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 102. Withdrawal of the rejection is requested.

Claims 1-13 and 21 have been rejected under 35 U.S.C. 103(a) as unpatentable over Kim *et al.*, in view of Baranov *et al.* (1993) Methods in Enzymology 217:123-142). The Office Action states that the difference between the instant claims, and Kim *et al.*, is the absence of polyethylene glycol, and states that Baranov *et al.* disclose a method of *in vitro* protein synthesis in reaction mixes that are substantially free of polyethylene glycol. It is further stated that it would have been obvious to combine the methods of Kim *et al.* and Baranov *et al.*, because both references are concerned with methods of producing maximal amounts of polypeptide using cell free expression systems.

Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references. The present invention is based on the extraordinary discovery that reaction conditions for cell-free synthesis can be manipulated in such a way as to provide for oxidative phosphorylation, as evidenced by the significant synthesis of polypeptides even in the absence of an exogenous energy source.

The ability to activate oxidative phosphorylation could not have been predicted by one of skill in the art, and could not have been predicted to arise from the combination of reaction conditions set forth by Applicants.

Although the art may have taught any number of individual reaction conditions, in this matter the synergistic result is clearly far greater than the sum of the various components. For example, in Baranov *et al.*, although certain reaction conditions left out PEG, there is no hint or

indication in the paper that this was a benefit. The paper provides a smorgasbord of reaction conditions, but does not provide an actual comparison of synthesis for reactions that differ only in the absence or presence of PEG.

One of skill in the art would not be motivated to combine the teaching of Kim *et al.* and Baranov *et al.* First, there is no indication in the art that any combination of reaction conditions could have provided for activation of oxidative phosphorylation. Further, there was no reason to believe that the absence of PEG would have improved synthesis in the reaction. In fact, as evidenced by Kim *et al.* (1996) Eur. J. Biochem. 239:881-886; or Kawarasaki *et al.* (1998) J. Biotechnol. 61:199-208 (abstracts attached), the literature taught that the inclusion of PEG increased polypeptide synthesis, and it would be desirable to include it in cell-free reactions.

One of skill in the art could not have predicted the synergy that is observed with the present combination of reaction conditions, which allows the activation of oxidative phosphorylation and subsequent improvements in yield of synthesized polypeptides.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention is not taught or suggested by the cited combination of references. Withdrawal of the rejections is requested.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-273.

Respectfully submitted,
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